Attorney Docket No. P63763US0
Application No.: 09/341,700

Remarks/Arguments:

Claims 59-78 are pending in this application.

Claims 70-77 were examined. Claims 59-69 and 78 were withdrawn from prosecution pursuant to restriction, which was traversed (Paper No. 22, filed October 30, 2001), the traversal being maintained, hereby.

According to the Office Action, claims 70-77 are rejected under 35 USC 103(a) for allegedly having been obvious over the combined teachings of five (5) references, i.e., James, Stull, Probst, Crooke, Baracchini, and de la Monte.

First of all, the rejection is fatally flawed since it relies on teachings in Baracchini (US Pat. No. 5,810,154) based on its (§120) *priority* date of April 16, 1996 (i.e., its April 8, 1997, filing date being later than the (§119) priority date of the subject application). The *teachings* (disclosure) relied on in Baracchini are *not* entitled to the April 16, 1996, priority date.

Baracchini is a *continuation-in-part* of the (§120) priority application filed April 16, 1996, i.e., ser. no. 628,731 (now US Pat. No. 5,807,838). Teachings in Baracchini that are relied on to reject the present claims (i.e., Baracchini columns 6-9) are not disclosed in the '731 priority application. In particularly, the statement of rejection alleges (Office Action page 5, last incomplete paragraph) (*emphasis added*):

> Baracchini et al teach methods for the preparation of antisense oligonucleotides comprising at least 8 residues, [and] *a maximum of twelve elements* . . . optionally comprises internucleotide, sugar and/or nucleobase modifications for enhancing stability against nucleases, *which sugar modifications include 2'-O-methoxyethoxy substituted sugars.*

Baracchini (column 8, lines 57-62) does expressly teach a preference for sequences having *12 nucleotides*, i.e.,(***emphasis added***):

> The oligonucleotides in accordance with this invention preferably comprise from about 8 to about 30 nucleotides. It is more preferred that such oligonucleotides comprise from about *12* to 25 nucleotides. As will be appreciated, a nucleotide is a base-sugar combination suitably bound to an adjacent nucleotide through phosphodiester or other bonds.

However, this teaching represents a *change* from the teachings of the Baracchini (§120) priority application (as found in US Pat. No. 5,807,838), i.e., (*emphasis added*):

> The oligonucleotides in accordance with this invention preferably comprise from about 8 to about 30 nucleotides. It is more preferred that such oligonucleotides comprise from about *15* to 25 nucleotides. As will be appreciated, a nucleotide is a base-sugar combination suitably bound to an adjacent nucleotide through phosphodiester or other bonds.

Baracchini (column 7, lines 57-62) also expressly teaches sugar modifications, which include 2'-O-methoxyethoxy substituted sugars, i.e.:

> A preferred [sugar] modification includes *2'-methoxyethoxy* [2'-O-CH_2 CH_2 OCH_3, *also known as 2'-O-(2-methoxyethyl)*] (Martin et al., Helv. Chim. Acta 1995, 78, 486).

However, this express teaching is not found in the the Baracchini (§120) priority application.

Accordingly, not being found in the (§120) priority application, the teachings of Baracchini relied on in the §103(a) rejection have an effective date as prior art only as of April 8, 1997, the date of filing application no. 835,770, which application was first to include the teachings relied on. Since the effective filing date (under §119) of the subject application, January 31, 1997, is prior to the effective date of the teachings in Baracchini relied on to reject the claims under §103(a), the rejection cannot be maintained and, so, is in order for withdrawal.

Moreover, the §103(a) rejection cannot be maintained for the reasons as follows.

James (previously cited) reviews the developments of antiviral antisense nucleic acids and ribozymes. The reference also discloses some modifications of oligonucleotides; but, it discloses no information as to which primary sequence should be selected or avoided for the oligonucleotide.

Stull (newly cited) teaches a method to facilitate the optimal selection of antisense oligonucleotide targets. The method relies on the use of three thermodynamic indices to calculate the free energy (ΔG) of secondary structure formation and not to calculate G-contents. These indices include a secondary structure score (Sscore) to estimate the strength of local mRNA secondary structures at the antisense oligonucleotide-target site, a duplex score (Dscore) to estimate the (ΔG) formation (free energy) for the antisense to mRNA target suplex, and a competition score (Cscore), which is the difference between the Dscore and the Sscore. Thus, the ΔG calculated does not tell anything about the G-content; rather, it indicates the free energy of a duplex, either within the mRNA or between the mRNA and an antisense oligonucleotide. As such, from Stull one skilled in the art could not have deduced a method for the preparation of effective antisense oligonucleotides having the parameters as presently claimed (claim 70). Stull does not teach or suggest that an antisense oligonucleotide should include the features a) to e) recited in present claim 70.

Further, Stull does not teach or suggest that consecutive guanosines should be avoided. On the contrary, there are a couple of oligonucleotides efficient in (according to Stull) inhibiting the expression of a target sequence comprising even five consecutive guanosines (see oligonucleotides

ss6 in Stull Table 1), four consecutive guanosines (see oligonucleotide F and M in Stull Table 3), or two series of three consecutive guanosines (see ISIS1574 in Stull Table 4).

Additionally, the oligonucleotide "G" in Stull Table 3 does not comply with the ratio

[3H-bond-R]/[3H-bonds-R + 2H-bonds-R],

which should lie between 0.33 and 0.86, since the ratio of the given oligonucleotide is 0.93. Therefore, Stull effectively teaches away from the presently claimed invention.

Accordingly, it would not have been obvious (1) that consecutive guanosines in oligonucleotides should be avoided or (2) that the ratio

[3H-bond-R]/[3H-bonds-R + 2H-bonds-R],

should lie between 0.33 and 0.86.

Therefore, Stull effectively teaches away from the presently claimed invention.

The statement of rejection acknowledges (Office Action page 4, last paragraph) that none of the primary references teaches a relationship between cellular cytotoxicity, on the one hand, and guanosine content, on the other. To overcome the deficiency of the primary references, the statement of rejection relies on Probst.

Probst (newly cited) discloses information about the "G-tetrad in antisense targeting." The reference discloses that G-rich oligonucleotides show the sequence-unrelated antiproliferative effect of phosphorothioated oligonucleotides, especially in a completely phosphorothioated form. According to Probst there are two mechanisms involved: (1) possible effects on the enzyme telomer terminal tranferase (telomerase) and (2) the fact that G-rich motives can form four-stranded

complexes. Probst, then, speculates that, as some proteins seem to have a high affinity for G-rich oligonucleotides, this high affinity binding to cellular or extra-cellular proteins could lead to non-antisense, but sequence-specific, effects. Therefore, Probst is neither positive nor negative about the presence of G-tetrads. Furthermore, the reference does not teach (1) avoiding the presence of two or more G-triads and (2) incorporating the features a), b), d), and e) of claim 70.

Crooke discloses therapeutic applications of oligonucleotides. Although some of the compounds disclosed fulfill the criteria of features a) to e) of claim 70, Crooke also discloses oligonucleotides that do **not** fulfill the criteria. Therefore, contrary to allegations contained in the statement of rejection, there is no teaching concerning a rational design of an antisense oligonucleotide with respect to the features a) to e) of the present claims.

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

As explained, above, the Baracchini teachings relied on are not prior art against the instant claims. Moreover, however, the reference does not disclose antisense-oligonucleotide modulation of a multi-drug-resistant associated protein.

Some sequences do fulfill the criteria of features a) to e) of claim 70. On the other hand, for example, sequences 1, 2, 11 and 26 do not, because each contains a GGGG-element. Baracchini

prefers such oligonucleotides (Baracchini column 8, line 36). Therefore, Baracchini does not teach avoiding GGGG elements, or two or more GGG elements, allegations to the contrary in the statement of rejection notwithstanding. *Hedges, supra. Fine, supra.*

In connection with de la Monte, as correctly set forth in the statement of rejection, the reference teaches the conjugation of hormones with antisense oligonucleotides; but, this is not a relevant point with respect to the presently claimed invention.

The allegation that Probst teaches avoiding "G-rich motives" (Office Action page 6) is incorrect. As discussed above, Probst discusses mechanisms of the action of G-tetrads (not of G motives, in general). There is not even a clear teaching in Probst to avoid G-tetrads, because Probst teaches that they can have sequence-specific (although non-antisense) effects. Probst states that such oligonucleotides facilitate cellular uptake and, if it all, teaches avoiding completely phosphoro thioated oligonucleotides. There is no information provided on cellular toxicity in relation to G-quartets or G-triplets.

As such, the statement of rejection relies on hindsight reconstruction in order to combine the references' teachings in the rejection under §103(a). In contrast to the allegation (Office Action page 6, last five lines), nothing in the references relied on teaches or suggests that prior art oligonucleotide sequences "routinely lacked" sequence configurations with G-tetramers or two or more G-triplets.

Crooke, Baracchini, and Skull do disclose *some* oligonucleotides having sequence configurations that lack G-tetramers and or two or more G-triplets; however, none of these references discloses such configurations *exclusively*. The cited references disclose oligonucleotides that *include*

G-quartets and two or more G-triplets, which cannot be ignored, as in the statement of rejection, in analyzing the references under §103(a).

> When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. . . There must be something in the prior art to suggest the desirability, and thus the obviousness, of making the combination." [*Citation omitted.*]

Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985). The fact that all elements of a claimed invention are known does not, by itself, make the combination obvious. *Ex parte Clapp*, 227 USPQ 972 (BPA&I 1985). To support a rejection for obviousness based on the combination of separate prior art teachings, the USPTO "must identify specifically the principles known to one of ordinary skill, that suggests the claimed combination." *In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998).

When correctly interpreted under §103(a), the cited references are shown to neither teach nor suggest avoiding avoiding antisense oligonucleotides containing G-quartets or two or more G-triplets.

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Favorable action is requested.

Respectfully submitted,

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